Prospective associations between cardiac stress, glucose dysregulation and executive cognitive function in Black men: The Sympathetic activity and Ambulatory Blood Pressure in Africans study

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Abstract: Objective: Glucose dysregulation is an independent risk factor for cardiovascular and neurodegenerative disease development through synaptic dysfunction resulting in cognitive decline. The aim of this study was to study the interplay between impaired glycaemic metabolism (hyperglycaemia and insulin resistance), cardiac stress (cardiac troponin T and N-terminal brain natriuretic peptide) and executive cognitive function prospectively, in a bi-ethnic sex cohort. Methods: Black and White teachers (N = 338, aged 20–63 years) from the Sympathetic activity and Ambulatory Blood Pressure in Africans study were monitored over a 3-year period. Fasting blood samples were obtained for cardiac troponin T, N-terminal brain natriuretic peptide, glycated haemoglobin and the homeostatic model assessment-insulin resistance for insulin resistance. The Stroop colour-word conflict test was applied to assess executive cognitive function at baseline. Results: Over the 3-year period, Black men revealed constant high levels of cardiac troponin T (4.2 ng/L), pre-diabetes (glycated haemoglobin $> 5.7\%$) and insulin resistance (homeostatic model assessment-insulin resistance >3). $\%\Delta$ Glycated haemoglobin was associated with $\%\Delta$ insulin resistance ($p < 0.001$) and increases in $\%\Delta$N-terminal brain natriuretic peptide ($p = 0.02$) in Black men only. In the latter, baseline Stroop colour-word conflict test was inversely associated with $\%\Delta$ cardiac troponin T ($p = 0.001$) and $\%\Delta$ insulin resistance levels ($p = 0.01$). Conclusion: Progressive myocyte stretch and chronic myocyte injury, coupled with glucose dysregulation, may interfere with processes related to interference control in Black men.

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Prospective associations between cardiac stress, glucose dysregulation and executive cognitive function in Black men: The SABPA study

Running head: Cardiac stress, insulin resistance and cognition

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ABSTRACT

Objective

Glucose dysregulation is an independent risk factor for cardiovascular and neurodegenerative disease development through synaptic dysfunction resulting in cognitive decline. The aim of this study was to study the interplay between impaired glycemic metabolism (hyperglycemia and insulin resistance (IR)), cardiac stress (cardiac troponin T (cTnT) and N-terminal brain natriuretic peptide (NT-proBNP)) and executive cognitive function prospectively, in a bi-ethnic sex cohort.

Methods

Black and White teachers (N=338, aged 20-63 years) from the Sympathetic Activity and Ambulatory Blood Pressure in Africans study were monitored over a three-year period. Fasting blood samples were obtained for cTnT, NT-proBNP, glycated hemoglobin (HbA1c) and the homeostatic model assessment (HOMA-IR) for insulin resistance. The STROOP colour-word conflict test (STROOP-CWT) was applied to assess executive cognitive function at baseline.

Results

Over the three-year period Black men revealed constant high levels of cTnT (≥4.2ng/L), pre-diabetes (HbA1c>5.7%) and IR (HOMA-IR>3). HbA1c was associated with IR ($p<0.001$) and increases in ΔNT-proBNP ($p=0.02$) in Black men only. In the latter, baseline STROOP-CWT was inversely associated with cTnT ($p=0.001$) and IR levels ($p=0.01$).

Conclusion

Progressive myocyte stretch and chronic myocyte injury, coupled with glucose dysregulation may interfere with processes related to interference control in Black men.

Keywords: NT-proBNP; cardiac troponin; hyperglycemia; insulin resistance; cognition

INTRODUCTION

The importance of blood glucose regulation in cardiovascular disease (CVD) prevention has been emphasized.[1] Hyperglycemia persists during conditions of chronic stress and vascular injury.[2,3] One of the causes of hyperglycemia, insulin resistance (IR), plays a detrimental role in CVD, as it independently predicts prevalent and incident CVD development.[4] Further, studies also show that chronic hyperglycemia (glycosylated hemoglobin (HbA1c) ≥5.6)) is associated with subclinical myocyte injury.[5]

Injury to cardiac myocytes has been identified as a major contributing factor for cardiac dysfunction and –failure.[6] Myocyte injury is the main stimulus for the release of cardiac troponin T (cTnT) from the myofibrils in cardiac muscle.[7] An association between cTnT and N-terminal pro-B-type natriuretic peptide (NT-proBNP) was reported in individuals with the metabolic syndrome.[8] In Black men from the SABPA cohort, cTnT was also associated with NT-proBNP, which may indicate increased cardiac wall strain in our population group.[9]

There is increasing evidence to suggest a role of cardiac stress in the development of neurodegenerative diseases as cTnT and NT-proBNP are independently associated with cognitive decline.[10,11] Mirza et al., (2015) reported higher NT-proBNP is related to poorer performance in multiple cognitive tests (STROOP-colour word conflict test (STROOP-CWT)) while Gluck et al. (2013) further showed that the STROOP-CWT, was associated with impaired glucose regulation.[10,12] Furthermore, executive cognitive function, assessed with the STROOP-CWT, differed significant between individuals with type 2 diabetes and individuals with normal glucose metabolism.[13]

The aim of this study was therefore to study the interplay between impaired glycemic metabolism, cardiac- and cognitive function. We assessed the relationship between changes (Δ) in cardiac stress risk markers (cTnT and NT-proBNP), glycemic metabolism (HbA1c, IR) and a cognitive test score in a bi-ethnic sex cohort over a three-year period.

METHODS

The Sympathetic and Ambulatory Blood Pressure in Africans (SABPA) prospective cohort study included urban Black and Whites teachers from the Dr Kenneth Kaunda Education District of the North-West Province of South Africa.[14] This selection was chosen to ensure a similar socio-economic class.[15] From February to May (2008 and 2009), 2170 teachers were invited to participate (Figure 1). Participants aged 20-65 years were assessed for eligibility, with 407 being included into phase I of the study. Phase II of the study was conducted after a period of three years from February to May (2011 and 2012). The successful follow-up rate was 87.8% (359 participants; aged 20-63 years). Reasons for non-participation in phase II of the study were pregnancy (N=2), death (N=6) and drop outs (N=42). To avoid bias pertaining to cardio-metabolic risk, participants with a HIV positive status (N=21) were excluded for the purpose of this study.[15] Ultimately 338 (152 Black and 186 White) participants remained for the present study.

Informed consent was obtained from all the participants prior to the commencement of the study. The Ethics Review Board of the North-West University, Potchefstroom Campus (NWU-00036-07-S6) gave ethical approval and the study also complied with the Declaration of Helsinki's ethical guidelines, revised in 2008.[16]

Experimental methods and data collection

All clinical assessments were obtained over 48 hours. Each participant was connected to the Cardiotens CE120® (Meditech, Budapest, Hungary) apparatus and accelerometers in order to measure 24-hour ambulatory blood pressure (ABPM), electrocardiogram (ECG), as well as 24-h physical activity. The correct cuff sizes were applied to the non-dominant arm of each participant. The participants were transported to the Metabolic Unit Research Facility at the North-West University at approximately 16:30 where they were introduced to the experimental set-up. Each participant received his/her own private bedroom and a standardized dinner. Demographic and General Health questionnaires were also completed. The participants were advised to fast and rest from 22:00 for the next day's clinical measurements.

At approximately 07:30 the following morning, the 24-hour ambulatory devices were disconnected where after anthropometric and clinical measurements followed. All resting ECG's, blood sampling and STROOP-CWT measures were obtained after the participants had been in a semi-recumbent position for approximately 30-45 minutes. Once the assessments were completed, the participants received breakfast and were transported back to their respective schools. Immediate feedback was also provided.

Lifestyle determinants

Registered level II anthropometrists obtained the anthropometric measurements according to standardized procedures. The mean of three measurements was used to ensure accuracy. Inter- and intra-observer variability was found to be less than 10%. The Mosteller formula [weight (kg) x height (cm) ÷ 3600]½ was used to calculate the body surface area. The

participants' daily physical activity was also monitored (Actical® activity monitor; Mini Mitter Co., Inc., Bend, OR; Montreal, Quebec, Canada).

Biochemical measurements

Fasting blood samples were obtained by registered nurses from the ante-brachial vein utilizing a sterile winged infusion set and handled according to standardized procedures for storage at -80°C until analysis. Gamma-glutamyl transferase (γ-GT), an indicator of alcohol abuse, were analyzed with the enzyme rate method (Unicel DXC 800; Beckman and Coulter; Germany). Serum cotinine, an indicator of nicotine levels, were analyzed with the homogeneous immunoassay on Modular ROCHE Automized (Basel, Switzerland). Serum cTnT and NT-proBNP were analyzed with the high sensitive electrochemiluminescence immunoassay (ECLIA), Elecsys (ROCHE, Basel, Switzerland). In our sample, there were 91 (26.84%) undetectable cTnT values (<3 pg/ml) that were substituted for lower than detectable values. The inter- and intra-batch variability was 15% and 5.6% respectively for cTnT, and 4.6% and 4.2% for NT-proBNP. An ultra-high-sensitivity turbidimetric method (Unicel DXC 800, Beckman and Coulter, Germany) was used to analyze C-reactive protein. Serum tumor necrosis factor-alpha (TNF-α), was analyzed with the Quantikine High Sensitivity Human TNF-α Enzyme linked immunosorbent assay (HS ELISA; R&D Systems, Minneapolis, MN USA). Despite serum handling within 30 minutes, the inter- and intra-assay variability for TNF-α was 15% and 17.8% respectively.

Fasting blood glucose samples were collected in sodium fluoride tubes and analyzed with the timed-end-point method (Unicel DXC 800, Beckman Coulter, Germany). The turbidometric inhibition immunoassay was used to determine HbA1c (Integra 400; Roche, Basil, Switzerland). Serum insulin was analyzed with the electrochemiluminescence immunoassay

(ECLIA; Elecsys 2010, Roche, Basel, Switzerland) with an intra-assay- and inter-assay precision of 2% and 2.8% respectively. The homeostatic model assessment (HOMA) was used to indicate insulin resistance (IR) and was measured with the following formula: fasting glucose x fasting insulin/405.[17]

Cardiovascular assessment procedures

As part of the SABPA study design 24-hour BP was measured at 30-minute intervals from 08:00 to 22:00 and at 60-minute intervals from 22:00 to 06:00.[18] The European Society of Cardiology criteria for hypertension were employed [average 24-hour systolic blood pressure (SBP) of ≥130mmHg and/or diastolic blood pressure (DBP) of ≥80mmHg].[15] The data was analyzed with the CardioVisions 1.19 Personal Edition software (Meditech, Budapest, Hungary). Participants had to record any abnormalities they experienced throughout the day, on a 24-hour diary card. The abnormalities included visual disturbances, headaches, nausea, fainting, palpitations and stress. The Norav NHH-1200® ECG (NORAV medical LTD PC 1200, Israel, Software version 5.030) was used to record the resting 10-lead ECG.

Executive cognitive function

Executive cognitive function was assessed with the STROOP colour-word conflict test (STROOP-CWT). The participants were shown a cardboard containing series' of five words in random orders describing a specific color, but written in different colors. The ink color of a given word had to be identified verbally. When participants are faced with the task to name the ink color of a word instead of reading the word, an interference is caused by the more automated task (reading the color represented by the word).[19,20] In order to perform the less automated task it is therefore required by the participants to inhibit this interference caused by the more automated task.[19,20] Participants had to guard against reading the color

represented by the word. They were also encouraged to progress as fast as possible within 1 minute, and were interrupted to correct wrong answers. An interference score (STROOP-CWT) was calculated that represents the number of correct answers produced during the fixed period of 1 minute. A lower score thus represents that the individual found it more difficult to inhibit the interference.[19] The same two scientists obtained STROOP-CWT scores of teachers at baseline. Participants received a monetary incentive according to their performance on completion of the task.

Statistical analyses

Statistical analyses were performed with Statistica version 13 (TIBCO Software Inc., Palo Alto, USA, 2018). Normal distributions were computed to reveal symmetrical data. Logarithmic transformations were used for variables with skewed distributions. Baseline characteristics of the two ethnic groups were determined with independent t-tests. Chi-square tests (X^2) were used to determine prevalence as well as proportions. Single two-way general linear model interaction on main effects (ethnicity x sex) were computed for all cardiovascular risk markers, independently of a priori defined covariates.[15] Dependent t tests were used to calculate differences over time in each ethnic group. Percentage changes over time (%Δ) were calculated by using the formula: Δ = (follow-up – baseline)/baseline*100. McNemar's case-control tests were used to demonstrate changes when participants without diabetes (negative) at baseline become positive at follow-up; and diabetes-positive people at baseline recover to negative at follow-up. Forward stepwise regression analyses determined associations between dependent variables (ΔcTnT, ΔNT-proBNP, ΔHbA1c, ΔHOMA-IR and baseline STROOP-CWT) and independent variables (ΔcTnT, ΔNT-proBNP, ΔHOMA-IR and baseline STROOP-CWT) and additional covariates (inflammation) in several separate

models. For all of the above-mentioned analyses, significant values were noted when adjusted $R^2 \geq 0.25$ and $p \leq 0.05$.

RESULTS

Cross-sectional data analyses

Table 1 represents the clinical characteristics of the South African bi-ethnic sex cohort at baseline. Blacks had higher γGT, HbA1C, insulin and blood pressure values than whites. In turn, higher body surface area, physical activity, STROOP-CWT scores and cTnT levels were found in the Whites. More Blacks than Whites showed hyperglycemia (HbA1c>5.7%), compatible with a pre-diabetic state (62% vs 31%; p<0.001).

Significant interactions with sex were revealed for NT-proBNP [F(1,316), 8.19, p=0.005], cTnT [F(1,322), 12.44, p<0.001] and with ethnicity for insulin [F(1,324), 4.40, p=0.04]. Furthermore, interactions between ethnicity and sex were revealed for cognitive interference [F(1,324), 97.20, p<0.001]; [F(1, 324), 21.73, p<0.001] that motivated further stratification into ethnic-sex groups.

Longitudinal data analyses

A total of 33 participants had incomplete data for the main variables that included HbA1c (N=8), HOMA-IR (N=4), cTnT (N=9), NT-proBNP (N=11) and STROOP-CWT (N=1). Participants with incomplete data (N=33) were however included in all analyses as their exclusion did not change the outcome of the results.

Over the three-year period, insulin and IR decreased whereas NT-proBNP increased in Blacks and Whites (Supplementary Table S1). Additionally, Whites revealed decreases in

cTnT and resting glucose. In Black men, ΔNT-proBNP increased over the three-year period, whereas no significant % changes (Δ) were revealed for cTnT, HbA1c and IR (Table 2). In Black men, incidence of diabetes changed significantly over the three-year follow-up period (%Δ 7.36 [OR 0.1 (0.01, 0.78)], p=0.007). Here, 10 participants developed diabetes over the three-year period, with only 1 participant recovering from baseline to follow-up.

Forward stepwise regression analyses determined associations between changes (%Δ) in cardiac stress markers (NT-proBNP and cTnT), STROOP-CWT, IR and HbA1c over a three-year period. No associations were evident in women (of either ethnicity) and in White men; therefore, we will only report associations found in Black men as shown in Table 3. In Black men, constant high HbA1c (>5.7%) was associated with constant high IR (HOMA-IR>3) (Adj R^2 0.28, β=0.43; 95% CI 0.22 to 0.64; p<0.001) as well as increases in ΔNT-proBNP (Adj R^2 0.28, β=0.26; 95% CI 0.05 to 0.48; p=0.02). Also in Black men, baseline STROOP-CWT score was inversely associated with constant high cTnT (>4.2ng/mL) (Adj R^2 0.24, β= -0.36; 95% CI -0.57 to -0.15; p=0.001) and constant high IR (Adj R^2 0.24, β= -0.28; 95% CI -0.49 to -0.06; p=0.01).

DISCUSSION

The aim of this study was to determine whether changes in markers of cardiac stress were associated with changes in insulin resistance, hyperglycemia and a cognitive test score in a bi-ethnic male and female cohort. Over a three-year period cardiac stress (NT-proBNP and cTnT) associated with dysregulated glucose metabolism (IR and hyperglycemia) may interfere with the ability to inhibit cognitive interference.

Executive cognitive function, cardiomyocyte injury and glucose metabolism

In this study, Blacks revealed a lower STROOP-CWT score than Whites indicating that Blacks had more difficulty to inhibit cognitive interference than Whites. One of many reasons why Blacks revealed lower STROOP-CWT scores than Whites might be explained by the inverse association found between STROOP-CWT with constant high (≥4.2ng/L) cTnT levels[21] in this study, as higher cTnT might lead to subclinical cerebral injury expressed as silent brain infarcts and white matter lesions on magnetic resonance imaging.[22] Wijsman et al., reported that participants with higher hs-cTnT levels had steeper STROOP-CWT declines over a period of 3.2 years.[23] Indeed, in Black men high levels of cTnT >4.2ng/L indicative of ischemic heart disease risk[24] was sustained that associated with reduced cardiac output[25] possibly leading to cerebral hypoperfusion resulting in executive functional decline.[21]

Other factors may also influence cognitive interference scores such as neural activation[26] rather than increased cerebral perfusion in low-level alcohol users when compared to non-users.[27] As alcohol use increases, the difficulty score pertaining to the STROOP-CWT increases[28] indicating that high levels of alcohol abuse[29] and neural activity[23] previously described in the Black cohort should be considered for the lower cognitive interference scores evident in the Blacks.

Cognitive interference was also inversely associated with IR in the current Black male cohort. Studies have shown IR to be associated with memory impairments and atrophy of brain regions leading to cognitive deficits.[30] Usually atrophy of these brain regions occur in early onset Alzheimer's disease (AD).[30] Indeed, individuals with diagnosed AD showed reduced resistance to cognitive interference[31] and hypo-activation of brain areas involved in this inhibitory control.[32] The exact mechanism of how peripheral IR affects cognitive inhibitory

control is however unclear. Numerous mechanisms leading to impaired cognition may apply including excessive amyloid beta accumulation and tau hyper-phosphorylation.[33] Therefore, regulation of blood glucose and correction of IR in clinical setting may be of crucial importance for improved cognitive control and health.

Dysregulated glucose and myocyte stretch

IR has been reported in Black women of South Africa before.[34] We expand current findings by showing moderate IR (HOMA-IR >3, <5)[35] also in Black men. Different cellular mechanisms may be involved in the pathogenesis of IR that includes inflammation.[36] The Insulin Resistance Atherosclerosis Study reported associations between the inflammatory marker, TNF-α with higher glucose levels and IR.[37] However, statistical adjustments of TNF-α in our study indicated that moderate IR was evident in Black men, independent of inflammation.

The association found between hyperglycemia and IR in our Black male/female cohort may underscore their pre-diabetic state (HbA1c >5.7%)[35] previously reported by Lammertyn et al., (2011).[38] Insulin is responsible for the regulation of metabolism as it promotes glycogen synthesis and glucose uptake into the cells while inhibiting glucose release into the circulation.[36] With IR, the tissues thus show reduced sensitivity to insulin-mediated biological activity.[36] This results in a disrupted balance between glucose uptake and release into the circulation leading to excessive glucose accumulation in blood vessels.[2,3]

Again increased neural activity or depressed heart rate variability in the SABPA Black cohort, particularly men[23,39] might be one mechanism to explain the chronic hyperglycemia. Indeed, non-dipping Black men revealed higher HbA1c values, and associations were

demonstrated between chronically elevated blood glucose and a blunted nocturnal blood pressure dipping.[38] The latter is indicative of autonomic dysfunction and volume overload.[40] NT-proBNP is a valuable marker to assess volume overload as it is released in response to myocyte stretch along with BNP that may lead to sympathetic nervous system inhibition, as well as the induction of natriuresis and diuresis.[41] In this study, we saw that constant elevated cTnT and HbA1c levels were associated with NT-proBNP increases. Other studies reported an association between chronic hyperglycemia and subclinical myocardial injury, as indicated by increased cTnT levels.[5] We cautiously suggest that progressive increases in NT-proBNP may act as compensatory protective mechanism against chronic hyperglycemia and cardiomyocyte injury in the current Black male cohort over a three-year period.

Limitations and Conclusion

Although this study is the first to represent associations between cardiac stress, hyperglycemia, IR and cognitive interference in Blacks, there are limitations. The results cannot be attributed to the African population at large as participants consisted of a small prospective cohort in South Africa. We did not perform a mechanistic study, so even plausible inferences about the interplay of discussed relationships must remain speculative. The clinical relevance of our findings needs to be shown beyond a three-year observation period.

In conclusion, as depicted in Figure 2, we propose that progression of mycoyte stretch is associated with chronic myocyte injury and hyperglycemia in Black men. Furthermore, hyperglycemia is associated with insulin resistance that may interfere with the inhibition of cognitive interference in these men. Therefore in Black men, progressive myocyte stretch and

chronic myocyte injury, coupled with dysregulation of glucose metabolism may interfere processes related to interference control.

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DECLARATION OF CONFLICTING INTERESTS

The authors declare no conflict of interest pertaining to the information of this manuscript.

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FIGURE LEGENDS

Figure 1: A South African bi-ethnic sex cohort.

Figure 2: Proposed mechanism of cardiac stress markers and glucose dysregulation associating with executive cognitive function in Black men.

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Prospective associations between cardiac stress, glucose dysregulation and executive cognitive function in Black men: The SABPA study

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KEY MESSAGES

- This longitudinal study is the first to assess the associations between glucose dysregulation, myocardial stress and –injury as well as executive cognitive function in a South African cohort.
- In Black men, chronic raised HbA1c levels associated with NT-proBNP upregulation and moderate insulin resistance over a three-year period.
- Executive cognitive function also inversely associated with moderate insulin resistance and chronic raised cTnT levels in Black men.
- Progressive myocyte stretch and chronic myocyte injury, coupled with glucose dysregulation may interfere with processes related to interference control in Black men.

Table 1: Clinical characteristics of a South African bi-ethnic sex cohort at baseline.

Variables	Africans (N=152)	Caucasians (N=186)	p-values
Confounders			
Age, years	44.65 ± 8.13	46.58 ± 9.87	0.053
Body surface area, m^2	1.92 ± 0.22	2.01 ± 0.29	0.001
TEE, kcal/day	2678.06 ± 814.21	3155.06 ± 1672.30	0.002
Cotinine, ng/Ml	26.71 ± 60.86	24.05 ± 81.01	0.739
γGT, U/L	65.74 ± 82.48	28.02 ± 38.28	<0.001
Potential diabetes risk markers			
Glucose, mmol/L	5.71 ± 2.17	5.71 ± 0.83	0.976
HbA1C, %	6.08 ± 1.19	5.53 ± 0.43	<0.001
Insulin, uU/mL	14.96 ± 10.35	12.26 ± 8.70	0.010
HOMA-IR	3.87 ± 3.26	3.29 ± 2.90	0.083
Cognition			
STROOP-CWT score	48 ± 11	63 ± 13	<0.001
Cardiovascular characteristics			
24h SBP, mmHg	132 ± 17	125 ± 12	<0.001
24h DBP, mmHg	83 ± 11	77 ± 8	<0.001
NT-proBNP, pg/mL	43.50 ± 45.59	46.35 ± 47.03	0.580
cTnT, pg/mL	4.90 ± 2.81	5.68 ± 3.60	0.031
C-reactive protein, mg/L			
TNF-alpha, pg/mL			
Hyperglycemic, N (%)	93 (62.00)	57 (30.65)	<0.001
Moderate IR, N (%)	71 (47.33)	76 (41.08)	0.252

Medication usage			
Hypertension, N (%)	45 (35.43)	23 (13.45)	0.200
Anti-diabetic, N (%)	9 (0.07)	8 (0.05)	0.358

Data are presented as mean ± SD, median (95% CI) or number of participants (%). Abbreviations: γGT, Gamma glutamyl transferase; TEE, total energy expenditure; HbA1C, glycated hemoglobin; HOMA-IR, Homeostatic model assessment-Insulin resistance; STROOP-CWT, STROOP-colour-word conflict test score; SBP, systolic blood pressure; DBP, diastolic blood pressure; NT-proBNP, N-terminal pro-b-type-natriuretic peptide; cTnT, cardiac troponin T; TNF-alpha, tumor necrosis factor alpha. Hyperglycemic defined as HbA1c>5.7% and moderate insulin resistance defined as HOMA-IR>3 (33).

Table 2: Unadjusted differences over a period of 3-years in Black men.

	Black men (N=77)		
Variables	**Baseline; Follow-up**	**Difference**	**p-value**
Glucose, mmol/L	6.13; 6.07	-0.07	0.727
Insulin, uU/mL	15.69; 13.41	-2.28	0.086
HOMA-IR	4.38; 3.59	-0.79	0.074
HbA1C, %	6.27; 6.31	+0.04	0.784
cTnT, pg/mL	5.59; 5.36	-0.23	0.570
NT-proBNP, pg/mL	**36.12; 49.13**	**+13.01**	**0.039**
†Diabetes: % Δ [OR (95% CI)], p	7.36 [0.1 (0.01, 0.78)], 0.007		
†Diabetes *(BL +, FU -) / (BL -, FU +)*	1 / 10		

Data presented is unadjusted dependent sample T-tests. Abbreviations: HOMA-IR, Homeostatic model assessment-Insulin resistance; HbA1C, glycated haemoglobin; cTnT, Troponin T; NT-proBNP, N-terminal pro-Brain natriuretic peptide. †McNemar chi-square equation values are presented as percentage difference over three years' time followed by the Odds Ratio (±95% Confidence Interval). (BL +, FU -), frequency at baseline positive but negative at follow-up; (BL -, FU +), frequency at baseline negative but positive at follow-up.

Table 3: Independent associations between cardiac stress markers, insulin resistance and cognitive interference scores on in a Black male cohort.

	Black men (N=77)				
	ΔNTproBNP	**ΔcTnT**	**STROOP-CWT**	**ΔHOMA-IR**	**ΔHbA1C**
	β (95%CI)	**β (95%CI)**	**β (95%CI)**	**β (95%CI)**	
Adjusted R^2	0.11	**0.25**	**0.24**	0.10	**0.28**
ΔNTproBNP	-	**0.31**** **(0.10; 0.52)**	NS	NS	**0.26*** **(0.05; 0.48)**
ΔcTnT	**0.30**** **(0.07; 0.52)**	-	**-0.36**** **(-0.57; -0.15)**	NS	NS
STROOP-CWT	NS	**-0.32**** **(-0.53; -0.11)**	-	**-0.26*** **(-0.50; -0.02)**	NS
ΔHOMA-IR	NS	NS	**-0.28*** **(-0.49; -0.06)**	**-**	**0.43†** **(0.22; 0.64)**

Data presented is adjusted for a priori covariates and tumor necrosis factor-alpha. Abbreviations: NT-proBNP, N-terminal pro-b-type-natriuretic peptide; cTnT, cardiac troponin T; STROOP-CWT, STROOP colour-word conflict test score at baseline; HOMA IR, Homeostatic model assessment-Insulin resistance; HbA1C, glycated haemoglobin. Superscript symbol shows the trend of significance:*$p \leq 0.05$; **$p \leq 0.01$; †$p \leq 0.001$.

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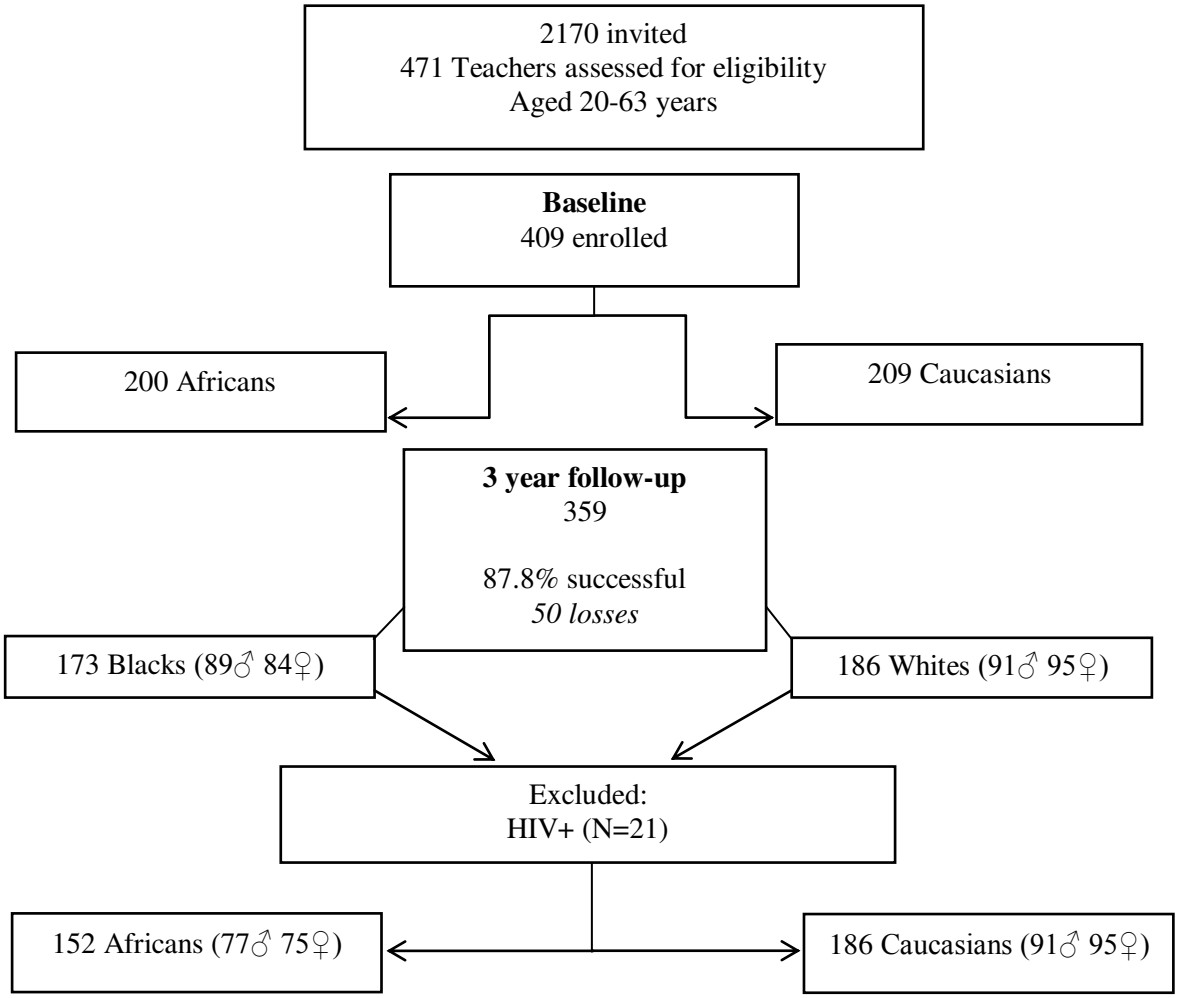

Figure 1: A South African bi-ethnic sex cohort.

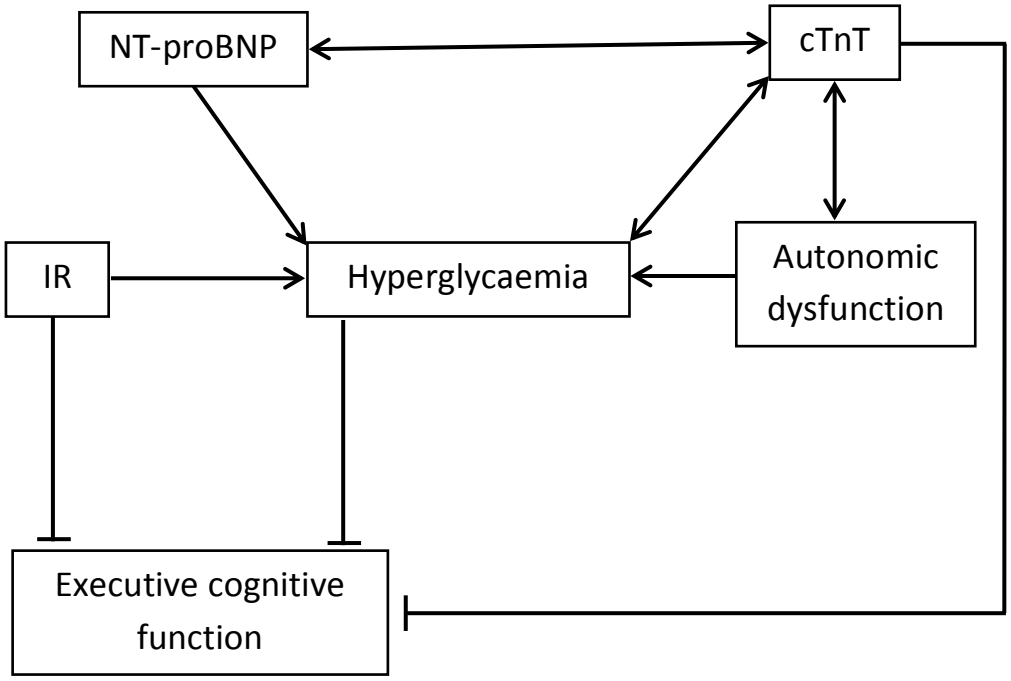

Figure 2: Proposed mechanism of cardiac stress markers and glucose dysregulation associating with executive cognitive function in Black men. Abbreviations: cTnT, cardiac troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide; ⟶ Arrows indicate that one variable leads to an increase of the next variable; ⟷Arrows indicate that positive associations exist between these variables; ⟙ Arrows indicate that one variable may lead to a decrease of the next variable.

Supplementary Table S1: Unadjusted differences over a period of 3-years in a Black and a White cohort.

	Blacks (N=152)			Whites (N=186)		
Variables	**Baseline; Follow-up**	**Difference**	**p-value**	**Baseline; Follow-up**	**Difference**	**p-value**
Glucose, mmol/L	5.71; 5.62	-0.09	0.523	**5.71; 4.43**	**-1.28**	**<0.001**
HbA1C, %	6.07; 6.18	+0.11	0.204	5.53; 5.59	+0.05	0.120
Insulin, uU/mL	**14.80; 12.19**	**-2.60**	**<0.001**	**12.26; 10.32**	**-1.94**	**<0.001**
HOMA IR	**3.83; 3.08**	**-0.75**	**0.004**	**3.29; 2.16**	**-1.13**	**<0.001**
NT-proBNP, pg/mL	**43.57; 57.67**	**+14.11**	**0.003**	**46.50; 83.29**	**+36.79**	**<0.001**
cTnT, pg/mL	4.89; 4.62	-0.27	0.352	**5.47; 4.89**	**-0.58**	**<0.001**

Data presented is unadjusted dependent sample T-tests. Abbreviations: HbA1C, glycated hemoglobin; HOMA IR, Homeostatic model assessment-Insulin resistance; NT-proBNP, N-terminal pro-b-type-natriuretic peptide; cTnT, cardiac troponin T.